Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs

[3-25-2011] The U.S. Food and Drug Administration is advising drug manufacturers of the potential formation of glass lamellae (glass fragments) in injectable drugs filled in small-volume glass vials[1]. Several drugs have recently been recalled due to this problem.[2]

Glass has many advantages over other packaging materials, but one well-known disadvantage is the potential for glass under certain conditions to shed thin, flexible fragments called “glass lamellae.” [3][4] These lamellae are shed from the interior surface of the glass container directly into the drug and are difficult to detect by visual inspection.

To date, no adverse events have been reported nor can any be directly attributed to this phenomenon. However, there is the potential for drugs administered intravenously that contain these fragments to cause embolic, thrombotic and other vascular events (e.g., phlebitis); and, when administered subcutaneously, to lead to development of foreign body granuloma, local injection site reactions, and increased immunogenicity.[5]

The following conditions have been associated with a higher incidence of the formation of glass lamellae:

- Glass vials manufactured by tubing process (and thus manufactured under higher heat). These vials are less resistant than molded glass vials and may shed lamellae more easily.[6] The processing conditions used to manufacture glass vials can be designed to mitigate the potential for later delamination.
- Drug solutions formulated at high pH (alkaline) and with certain buffers. Common buffers associated with lamellae formation include citrate and tartrate.[7]
- Length of time the drug product remains exposed to the inner surface of the container. The time duration has a direct correlation to the potential for glass lamellae formation to occur during the product shelf life.[3]
- Drug products with room temperature storage requirements. Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures.[8]
- Terminal sterilization has a significant effect on glass stability.[4]

The referenced literature, below, includes recommended actions to help prevent the formation of glass lamellae. For example, for products “at risk” the vial surface alkalinity can be minimized by proper selection of glass composition (e.g., highly resistant, non-alkaline earth borosilicate glass) appropriate selection and qualification of vendors, and proper quality control of the incoming vials. Accordingly, FDA advises drug manufacturers of products to re-examine their supplier quality management program with the glass vial manufacturers to assure that this phenomenon is not occurring. Further, the Agency reminds finished drug product manufacturers that current good manufacturing practice regulations require that drug containers not be reactive or additive so as to alter the safety or quality of the drug.[9][10]
See deviation reporting regulations for Field Alert Reports (21 CFR 314.81) and Biological Product Deviation Reports (21 CFR 600.14) http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm (epoetin alfa, methotrexate, hyaluronidase recombinant, and fluorouracil)


[9] 21 CFR 211.94, Drug product containers and closures